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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,489	04/03/2001	Sudhir Agrawal	047508.514 US2 (HYZ-075)	2089

23483 7590 09/14/2004

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 09/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,489	AGRAWAL ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *3-9,15-18,23-29,35-38 and 41-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10-14,19-22,30-34,39,40 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/13/01 & 5/16/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I, claims 1-5, 10-16, 19, 20 and 49 in the reply filed on July 14, 2004 is acknowledged.

2. Applicant asserts that requiring election of a single nucleotide sequence for search is improper and quotes part of MPEP 803.04. Applicant's attention is drawn to the paragraphs preceding the ones quoted in the response to the restriction requirement, particularly the second paragraph of MPEP 803.04, which states "*Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C.121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq.*"

3. There is no requirement that more than one sequence be examined, only a decision by the Commissioner that up to ten sequences may be examined, requiring election of a single sequence does not constitute an improper restriction requirement. SEQ ID NO: 3 and SEQ ID NO: 4 are independent and distinct inventions because they do not have identical sequences and hence do not have identical structures. Search of more than one nucleotide sequence is burdensome because of the complex nature of

the search in terms of computer time needed to perform the search and the subsequent analysis of the search results by the examiner. The large amount of computer time required to perform a sequence search and the time required by the examiner to interpret sequence search results allows only one sequence to be searched. Currently the office is limiting all applicants to a single antisense sequence.

4. Applicant also requests rejoinder of the claims directed to XPA and XPG and assert that XPA and XPG perform the same function and are searchable together. While XPA and XPG may both act in the first step of nucleotide excision repair they are not identical and a search of patent and non-patent literature for XPA would not retrieve all references related to XPG. Even if two genes share a common functionality, they are still two different genes with unique structures, as evidenced by their separate sequences and are independent of each other and thus patentably distinct. If this were not the case, then art that reads on any nucleotide excision repair gene would anticipate any claims drawn to XPA or XPG. Since XPA and XPG are independent and distinct genes that have distinct structures, restriction between the two is proper.

5. Applicant requests reconsideration of the restriction requirement between independent claims 1 and 21, asserting the methods constitute identical steps and searching each of these methods would not constitute an undue burden. The method of claim 1 is meant to potentiate or enhance the effect of a cytotoxin on a cancer cell, implying that the cytotoxin has some effect on the cancer cell without the use of the claimed method. In contrast, the method of claim 21 is meant to be performed on a resistant cell and in fact claim 21 explicitly states that the cytotoxin is used in an amount

that is cytotoxic to a non-resistant cell. The method of claim 21 would not be necessary with a normal cell.

6. Although the two methods have similar steps, a full search of all limitations of one method would not automatically retrieve all references relevant to the other method. The claims as currently presented do allow a search to be somewhat co-extensive so the claims of group V will rejoined to the extent that they read upon the elected gene, the elected species and the nucleotide sequence that applicant has elected for group I. However, if the claims that make up the invention of group V are later amended so as to become divergent from the invention of group I, this restriction may be reinstated.

7. Claims 6-9, 17, 18, 26-29, 37, 38 and 41-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 3-5 and 23-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 15, 16, 35 and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, namely the antisense sequence recited in SEQ ID NO: 4, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 14, 2004.

The requirement is still deemed proper and is therefore made FINAL.

8. Claims 1, 2, 10-14, 19-22, 30-34, 39, 40 and 49 are being examined on the merits.

Priority

9. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e). The oath filed on August 17, 2001 makes a claim of priority to a provisional application, however 37 CFR 1.78 states that a proper claim under 35 USC 119(e) must be made in the specification or in an application data sheet and must be made within the later of 4 months of filing of the non-provisional application or 16 months after the filing date of the provisional application. No claim to priority is made in the specification and there is no application data sheet. Since the provisional application was filed on April 3, 2000 and since the instant application was filed April 3, 2001, the claim of priority to the provisional in the oath filed on August 17, 2001 is beyond both the 16-month date for provisional application and the 4-month date of the non-provisional application. As there is no proper claim for priority under 35 USC 119(e), the effective filing date is the filing date of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 10-14, 19-22, 30-34, 39, 40 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enhancing or potentiating the toxic effect of a cytotoxin on a cancer cell *in vitro* or *ex vivo*, does not reasonably provide enablement for performing the same method *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

10. The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

11. Claims 1 and 21 are drawn to a method of potentiating or enhancing the toxic effect of a cytotoxin on a cancer cell or a resistant cell using an antisense oligonucleotide against the XPA gene in combination with a cytotoxin. This is a method of treating cancer and claims 1 and 21 are not limited to any particular cancer or type of cancer. The method as claimed is also not limited to *in vitro* or *ex vivo* treatment but encompasses *in vivo* treatment in any organism, including humans. Claims 2-5, 10-16, 19, 20, 22, 30-34, 39 and 40 depend from either claim 1 or claim 21 and recite limitations with regard to the type of cytotoxin used, the genes and types of cancer

targeted and the physical characteristics of the antisense oligonucleotides. Claim 49 is another method broadly drawn to a method of potentiating or enhancing the toxic effect of a cytotoxin on a cancer cell with the sole limitation being that the target gene is involved in transcription coupled repair (TCR) or nucleotide excision repair (NER). The methods recited in these claims indicate that the nature of this invention is a technique for providing gene therapy.

12. The state of the art prior art is such that use of antisense techniques to modulate gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

13. The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (IDS of 9/13/01, reference A55) and Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

14. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of

delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

15. Opalinska et al. (Nature Review, 2002, vol 1, p. 503-514) state "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

16. Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression, as claimed. The specification provides examples of inhibition of gene expression in SV40-immortalized CS-B fibroblasts and CS-A cell lines, XP-A and XP-G

fibroblasts and A2780/CP70 cell culture, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell lines would not be applicable to delivery of oligonucleotides to any organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

17. Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in successful inhibition of expression of the target gene in a cancer cell. One of skill in the art would not know how to deliver oligonucleotides to an organism in such a way that would ensure an amount sufficient to modify or inhibit expression of a target gene is delivered to the proper cell.

18. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene such that the organism exhibits a loss of function phenotype.

19. The specification is not considered to provide the requisite guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic applications in any organism. The field of antisense therapeutics does not provide that guidance such that the skilled artisan would be able to practice the claimed therapeutic methods. The specification does not provide any specific guidance for overcoming the known unpredictable factors regarding the successful *in vivo* application of antisense.

20. Thus, while the specification is enabling for enhancing or potentiating the toxic effect of a cytotoxin on a cancer cell *in vitro* or *ex vivo*, the specification is not enabling for the broad claims of treating cancer in any organism as the art of inhibiting gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. In order to practice the claimed invention *in vivo* a number of variables would have to be optimized, including 1). The form of the oligonucleotide, for example,

whether to use a modified oligonucleotide with one or more backbone, sugar or base modifications, 2). the mode of delivery of the oligonucleotide to an organism that would allow it to reach the targeted cell, 3). the amount of oligonucleotide that would need to be delivered in order to allow inhibition of the expression of a target gene once it reached the proper cell and 4). ensuring the oligonucleotide remains viable in a cell for a period of time that allows inhibition of the gene to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense oligonucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1, 2, 10-14, 19-22, 30-34, 39, 40 and 49 are not enabled.

Claims 1, 2, 10-14, 19-22, 30-34, 39, 40 and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

21. Claims 1, 2, 10-14, 19-22, 30-34, 39, 40 and 49 are described in the previous enablement rejection. As described in the previous enablement rejection, the claims

encompass treatment of cancer in any organism, including humans, using antisense oligonucleotides against the XPA gene in combination with a cytotoxin such as cisplatin.

22. The specification teaches on pages 3 and 4 that cisplatin resistance is a problem with its use as an antitumor drug and resistance of tumor cells to cisplatin is related to up-regulation of DNA repair. XPA is one of several genes involved in nucleotide excision repair (NER), one type of DNA repair mechanism. The prior art has recognized a relationship between DNA repair genes and cisplatin sensitivity: NER deficient genes are more sensitive to cisplatin than repair-competent cells and conversely, increased NER capacity is related to resistance. With regard to one type of cancer, tumor cells that were resistant to cisplatin had increased levels of mRNAs related to several NER genes, including XPA.

23. The applicants have demonstrated that one human ovarian cancer cell line, A2780/CP70, treated with antisense oligonucleotides has decreased levels of XPA mRNA and that the treated cells are about 25% more resistant to cisplatin. (see example 3, pages 31 and 32)

24. The specification provides description of antisense oligonucleotides potentiating the effect of cisplatin in one cell line *ex vivo*, but does not provide adequate written description to support the use of antisense oligonucleotides complementary to XPA in order to treat all cancers. The term, "cancer" is a generic term for more than 100 diseases that are characterized by uncontrolled, abnormal growth of cells. The specification as filed does not provide any examples of *in vivo* treatment of any cancers

or any specific guidance as to how the skilled artisan would treat all forms of cancer practicing the method of the invention.

25. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

26. MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

27. The skilled artisan cannot envision the detailed structure of the encompassed antisense sequences, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

28. Therefore the full breadth of the claims does not meet the written description provision of 35 USC 112, first paragraph. The specifically disclosed structures of antisense sequences of oligonucleotides capable of inhibiting XPA expression are not sufficient to describe the full breadth of the claimed genus. The specifically disclosed cell lines described in the specification are not sufficient to describe the full breadth of the claimed genus of cancers. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 10, 19-22, 30, 39, 40 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Lu et al. (IDS of 5/16/2002, reference A1)

29. Claims 1 and 21 are drawn to a method of potentiating or enhancing the toxic effect of a cytotoxin on a cancer cell or sensitizing a resistant cell using an antisense oligonucleotide against the XPA gene in combination with a cytotoxin. Claims 2 and 22 state the method is performed with the cytotoxin cisplatin, claim 10 and 30 state the antisense oligonucleotide is directed to XPA gene, claims 19, 20, 39 and 40 state the types of cancers targeted, and claim 49 is a generic re-statement of claim 1 wherein the target gene is any gene involved in TCR or NER.

30. Lu et al. disclose that cisplatin toxicity can be potentiated by combining with antisense oligonucleotides targeted to XPA, a gene involved in NER, in SKBR-3 breast carcinoma cells. Lu et al. thus discloses all limitations of claims 1, 2, 10, 19-22, 30, 39, 40 and 49.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 10, 11, 14, 19-22, 30, 31, 34, 39, 40 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tortora et al. in view of Koberle et al. and Horton et al.

31. Claims 1, 2, 10, 19-22, 30, 39, 40 and 49 are described in the previous 102 rejection. Claims 11 and 14 limit claim 1 by stating the antisense oligonucleotide is directed to the coding region or the 3' untranslated region, respectively, of the XPA gene. Claims 31 and 34 limit claim 21 by stating the antisense oligonucleotide is directed to the coding region or the 3' untranslated region, respectively, of the XPA gene.

32. Tortora et al. (IDS of 5/16/2002, reference A2) teach that antisense oligonucleotides targeted to protein kinase A act synergistically with the cytotoxin cisplatin to inhibit the growth of cancer cells (see abstract and figure 2). Tortora et al. do not teach the use of antisense oligonucleotides targeted to the XPA gene.

33. Horton et al. (Nucleic Acids Research, 1995, vol 23, p 3810-3815) teach that while deficiency of DNA repair enzymes correlates with hypersensitivity to DNA damage the converse is also true and in cell lines and tumors increased levels of DNA repair enzymes correlate with drug resistance.

34. Koberle et al. (IDS of 9/13/01, reference A50) teach that reduced levels of XPA in testis tumor cells lines is responsible for the cell's increased sensitivity to cisplatin.

35. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Tortora et al. that antisense inhibition of gene expression has a synergistic effect with cisplatin in cancer cells by targeting the XPA gene.

36. Koberle et al. provide a motivation to modify the teaching of Tortora et al. by teaching on page 276, last paragraph that "specific inhibition of XPA could sensitise other types of tumours to cisplatin and thereby broaden the usefulness of its class of chemotherapeutic agents." Antisense gene therapy is a technique well-known to one of ordinary skill in the art to specifically inhibit gene expression and one of ordinary skill would be motivated to use it, as demonstrated by Horton et al., who state on page 3815: "it may be possible to enhance the cytotoxic effects of cisplatin and other DNA damaging chemotherapeutic agents by an antisense gene therapy approach."

37. A person of ordinary skill in the art would have had a reasonable expectation of success in modifying the method taught by Tortora et al. to enhance the effect of cisplatin on a cancer cell because Tortora taught their method to enhance the effect of cisplatin on a cancer cell using antisense inhibition of gene expression, a technique well

known to a person of ordinary skill in the art, and Koberle et al. teach that reduced levels of XPA expression increase the sensitivity of tumor cells to cisplatin, indicating that using antisense therapy to decrease the amount of XPA expressed in a cell would enhance the cytotoxic effect of cisplatin.

38. Therefore, the invention of claims 1, 2, 10, 11, 14, 19-22, 30, 31, 34, 39, 40 and 49 would have been obvious, as a whole, at the time the instant invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
September 8, 2004

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600